

REMARKS

In the present communication, claim 5 has been amended; claims 1-3 have been canceled; and no claims have been added. The amendments do not include new matter and are fully supported by the specification and claims as filed. Support for the amendments to claim 5 may be found throughout the specification, for example, in paragraphs [0094], [0110] and Figure 7. Accordingly, upon entry of the present amendment, claims 5-6 and 8-10 will be under consideration.

Rejections under 35 U.S.C. §102(b)

Applicant respectfully traverses the rejection of claims 1-3, 5, 6, 8 and 9 under 35 U.S.C. §102(b) as allegedly anticipated by Miyasaka et al. To anticipate, a single reference must inherently or expressly teach each and every element of the claimed invention. *In re Spada*, 15 USPQ2d 1655 (Fed Cir. 1990); and *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). MPEP § 2131.

The Office Action alleges that the pending claims recite only one active step; that of administering NG-monomethyl-L-arginine acetate (NMMA). The Office Action further alleges that the remaining limitations recited by the claims, which admittedly, Miyasaka et al. fail to disclose, are merely inherent outcomes of administering NMMA. Without acquiescing to the rationale presented in the Office Action, and in order to expedite prosecution of the instant application, Applicant has canceled claims 1-3 rendering the rejection moot as to such claims. Furthermore, with regard to claims 5, 6 and 8-10, Applicant has amended claim 5 to recite an additional active step. As amended, the claim recites as follows:

A method for inhibiting TGase activity of zymogen Factor XIIIa (FXIIIa) and/or tissue transglutaminase (tTGase) in a chondrocyte, comprising:

- a) contacting the chondrocyte with an effective amount of an inhibitor of a TNF α receptor-associated signaling factor (TRAF), wherein the inhibitor is NG-monomethyl-L-arginine acetate (NMMA); and
- b) detecting a decrease in TGase activity of zymogen Factor XIIIa (FXIIIa) and/or tissue transglutaminase (tTGase) in the chondrocyte, thereby inhibiting TGase activity of zymogen Factor XIIIa (FXIIIa) and/or tissue transglutaminase (tTGase) in the chondrocyte.

Applicant respectfully submits that Miyasaka et al. fail to disclose detecting a reduction of TGase activity of zymogen Factor XIIIa (FXIIIa) and/or tissue transglutaminase (tTGase) in a chondrocyte upon administration of NMMA as claimed. As such, Miyasaka et al. fail to teach each and every element of the claims and therefore fail to anticipate the claimed invention.

Accordingly, Applicant respectfully requests withdrawal of the rejection.

Rejections under 35 U.S.C. §103

Applicant respectfully traverses the rejection of claims 1-3, 5, 6 and 8-10 under 35 U.S.C. §103 as allegedly obvious over Nurminskaya et al., in view of Hashimoto et al., and further in view of Miyasaka et al.

The recent U.S. Supreme Court decision in the *KSR International v. Teleflex Inc.* (82 USPQ2d 1385), modified the standard for establishing a *prima facie* case of obviousness. Under the KSR rule, three basic criteria are considered. First, some suggestion or motivation to modify a reference or to combine the teachings of multiple references still has to be shown. Second, the combination has to suggest a reasonable expectation of success. Third, the prior art reference or combination has to teach or suggest all of the recited claim limitations. Factors such as the general state of the art and common sense may be considered when determining the feasibility of modifying and/or combining references.

As discussed above, with regard to claims 1-3, without acquiescing to the rationale presented in the Office Action, and in order to expedite prosecution of the instant application, Applicant has canceled claims 1-3 rendering the rejection moot as to such claims. Furthermore, with regard to claims 5, 6 and 8-10, Applicant has amended claim 5 to recite an additional active step. As amended, claim 5 recites detecting a reduction in TGase activity of zymogen Factor XIIIa (FXIIIa) and/or tissue transglutaminase (tTGase) in a chondrocyte upon administration of NMMA.

Applicant respectfully submits that the Office Action fails to present a *prima facie* case of obviousness as to the claims as amended because the cited references, whether considered individually or taken as a whole, fail to teach or suggest the invention of the amended claims. Applicant submits that the cited references fail to teach a method of inhibiting TGase activity of zymogen Factor XIIIa (FXIIIa) and/or tissue transglutaminase (tTGase) in a chondrocyte upon administration of NMMA as claimed. The Office Action admits that Nurminskaya et al. fail to disclose that blocking activation or activity of tTGase and FXIIIa would decrease apoptosis in pathological states. Similarly, the Office Action admits that Hashimoto et al. fail to disclose decreasing apoptosis in pathological states by administering NMMA to inhibit nitric oxide (NO). The Office Action attempts to cure the deficiency using the alleged teaching of Miyasaka et al. that NMMA successfully blocks the onset of arthritis and that NO stimulates apoptosis in chondrocytes.

Applicant submits that the cited references fail to teach inhibition of activation and/or activity of zymogen factor (FXIIIa) and tissue transglutaminase (tTGase) by administration of NMMA as claimed. Nurminskaya et al. fail to teach administering NMMA to a subject to inhibit activation and/or activity of zymogen factor (FXIIIa) and tissue transglutaminase (tTGase) in chondrocytes in the cartilage matrix. The teachings of Hashimoto et al., and Miyasaka et al. fail to remedy such deficiency because none of the cited references alone or in combination suggest or teach use of NMMA as an inhibitor of TGase activity. All of the references fail to specifically

teach inhibition of TGase activity of FXIIIa and tTGase upon administration of NMMA and subsequent detection of a reduction of TGase activity. As discussed in the specification (paragraph [0110] and Figure 7), Applicant determined the ability of NMMA to specifically inhibit the ability of both IL-1 and TNF α to induce TGase activity as well as observing an increase in matrix calcification as a result of increased TGase activity. In view of the references, one of skill in the art would have no motivation to detect such inhibition since NMMA was not a generally known inhibitor of such activity.

Further, Applicant submits that it is impermissible to use the claimed invention as an instruction manual or template to piece together the teachings of the prior art so that the claimed invention is rendered obvious. *In re Gorman*, 933 F2d 982, 987, 18 USPQ 2d 1885, 1888 (Fed. Cir. 1991). *See also Interconnect Planning Corp. v. Feil*, 774 F2d 1132, 1138, 227 USPQ 543, 547 (Fed. Cir. 1985)). It has been repeatedly decided that one cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention. *In re Fine*, 837 F2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988); *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992). The proper time frame to apply the obviousness test is that moment just before the invention was made, not whether the invention appears obvious to a judge or jury after they learn all about the invention. *Stratoflex Inc. v. Aeroquip Corp.*, 713 F2d 1530, 1538, 218 USPQ 871, 879 (Fed. Cir. 1983). As such, it is improper to use the claimed invention, in which TGase activity of Factor XIIIa and tissue transglutaminase (tTGase) is inhibited in a chondrocyte by contacting the chondrocyte with NMMA and subsequently detecting the activity of the TGase activity, to piece together the disclosures of Nurminkaya et al., Hashimoto et al., and Miyasaka et al., which fail to disclose inhibition of TGase activity by administration of NMMA.

Accordingly, for the foregoing reasons, Applicant respectfully requests the rejection be withdrawn.

In re Application of:
Robert Terkeltaub
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Conclusion

In view of the amendments and above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

No fees are deemed necessary with the filing of this paper. However, the Commissioner is hereby authorized to charge any other fees that may be due in connection with the filing of this paper, or credit any overpayment to Deposit Account No. 07-1896, referencing the above-identified docket number.

Respectfully submitted,

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